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Relationships between HMG-CoA reductase inhibitors (statin) use and strength, balance and falls in older people

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Abstract

Aims: To investigate associations between HMG-CoA reductase inhibitor (statin) use and muscle strength, balance, mobility and falls in older people.
Methods: Five hundred community-dwelling people aged 70–90 years provided information about their medication use and undertook tests of lower limb strength, postural sway, leaning balance (maximal balance range and coordinated stability tests) and functional mobility. Participants were then followed up for 12 months with respect to falls.
Results: After adjusting for general health in analyses of covariance procedures, statin users had poorer maximal balance range than non-statin users ($P = 0.017$). Statin and non-statin users did not differ with respect to strength, postural sway, mobility or falls experienced in the follow-up year.
Conclusion: In a sample of healthy older people, statin use was not associated with muscle weakness, postural sway, reduced mobility or falls. Statin users, however, had poorer leaning balance which may potentially increase fall risk in this group.

Introduction

Atherosclerosis and atherosclerosis-associated conditions, such as coronary heart disease and ischaemic cerebrovascular disease, are major causes of morbidity and mortality among middle aged and older adults in developed countries.[1–4] Hyperlipidaemia and low levels of high density lipoprotein cholesterol (HDL-C) increase atherogenic risk.[1,5] Multiple well-controlled clinical trials have

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Conflict of interest: The Physiological profile Assessment (NeuRA FallScreen) is commercially available through Neuroscience Research Australia.

documented the safety and efficacy of HMG-CoA reductase inhibitors (statins) in reducing fatal and non-fatal coronary heart disease events, strokes and overall mortality.[6]

Whilst clinical trials have demonstrated statins to be generally safe and well tolerated, there is emerging evidence that statins cause proximal muscle weakness with or without creatine kinase elevation.[7–11] Little is known about the mechanism of statin-induced muscle toxicity. Several theories have been proposed suggesting that myopathy is caused by metabolic abnormalities.[10,11] Flint *et al*. suggests that GTP-binding proteins' depletion caused by inhibition of mevalonate participates in statin myotoxicity.[12,13] Urso *et al*. found that statins plus exercise resulted in changes in gene expression for the ubiquitin proteasome pathway (UPP) whereas this did not occur in a control group or a statin without exercise group. UPP is responsible for protein transcription and degradation in skeletal muscle and if protein degradation is enhanced through this pathway, it may explain the mechanism underlying statin-related myotoxicity.[14,15]

Older adults have increased falls risk because of age-related muscle decline, impaired balance, co-morbidities, medication use and increasing frailty and it has been postulated that statins may exacerbate age-related muscle decline, potentially increasing falls risk.[8,16–23]

The evidence for an association between statin use and muscle weakness, however, is inconsistent. In a recent Tasmanian study, Scott *et al*. assessed percentage of lean muscle mass in arms and legs, isometric strength of quadriceps and hip extensors as well as falls risk in 774 statin and non-statin users and reported that statin users had a greater decline in strength, muscle quality and modest increases in fall risk scores. There were no significant differences between the type of statin used.[24] Other smaller studies have suggested that people experience difficulty walking and rising from a chair between 3 and 12 months after commencing statin therapy[8,9] and that proximal strength and other functional symptoms recover within 3 months of statin cessation.[8,9,11]

In contrast, other studies have found either small beneficial effects or no detrimental effects of stain use in older people. Agostini *et al*. found statin use to be associated with slightly improved performance in timed chair stands in a study of ambulatory, community-dwelling males (mean age 75 years).[25] Similarly, McDermott *et al*. found elderly statin users with peripheral arterial disease performed better in the 6-min walk, walking velocity test and summary performance score than elderly non-statin users,[26] and this improvement was sustained over time.[27] In those without peripheral arterial disease, there was no difference in strength measures between statin and nonstatin users.[26,27] Ashfield *et al*. found no association between statin use and grip strength in women and men aged 59–73 years.[28]

The conflicting evidence in relation to statin use and physical performance is possibly caused by inconsistencies in the types of functional tests used, sample sizes, co-morbidities and/or gender of participants.[8,9,25,26] Further, most previous studies have included only a limited range of physical performance measures and none has examined the relationship between statin use and prospectively measured falls.

The aims of this study, therefore, were to investigate: (i) whether there are significant associations between statin use and muscle strength, balance and mobility and (ii) whether statin use increases the risk of falls in community-dwelling older people.

Method

Participants

Five hundred community-dwelling people aged 70 to 90 years participated in the prospective cohort study with a 1-year follow-up for falls. They were randomly recruited from a cohort of 1037 community-dwelling men and women living in eastern Sydney and participating in the first stage of the Sydney Memory and Ageing Study (January 2006 to October 2007).[29]

Exclusion criteria were severe neurological, cardiovascular or major musculoskeletal impairments (determined at a baseline physiological assessment) that precluded participants from walking 20 m without a walking aid, and cognitive impairment determined by a score of <24 on the Mini-Mental State Examination (MMSE). All participants provided informed consent, approved by the University of New South Wales Human Studies Ethics Committee (HREC #05224).

Assessments

At baseline, all participants underwent an extensive assessment of medical, physical and cognitive measures by trained research personnel.[30]

Medical assessment

A complete medical history was recorded, including the presence of medical conditions, medication use and falls history. Participants brought containers for all current medications to the assessment and research staff recorded all medications, including the type and prescribed dosage. Statins used by those in the survey included fluvastatin, pravastatin, rosuvastatin, simvastatin and atorvastatin. Length of statin use and dosage regimens for the different

statins were not used in this analysis and no differentiation was made between the types of statin used.

Physical assessment

The Physiological Profile Assessment (PPA)[18] has been developed by the Falls and Balance Research Group at Neuroscience Research Australia, Sydney and uses an individual's physiological profile to estimate falls risk.[31,32] A standardised fall risk score is obtained from data collected from five measures of sensorimotor function with validity and reliability established in previous studies: (i) visual contrast sensitivity was assessed using the Melbourne Edge Test which requires the correct identification of the orientation of edges in 20 circular patches halved with reducing contrast, (ii) proprioception was measured using a lower limb-matching task. Participants were seated with their eyes closed and asked to align their lower limbs simultaneously on either side of a vertical acrylic sheet (60 × 60 × 1 cm) inscribed with a protractor and placed between the legs. Errors in alignment of the great toes were recorded in degrees. The average of five trials was recorded. (iii) Quadriceps strength was measured isometrically in the dominant leg, while participants were seated with the hip and knee flexed to 90 degrees. Participants were required to pull against the strain gauge – attached to a strap around the dominant leg, 10 cm above the ankle joint – with maximal force for 2–3 s with the best score out of two trials recorded. (iv) Simple reaction time was measured using a light as stimulus and a finger press as response. The average of 10 trials was recorded. (v) Postural sway was measured using a sway meter recording displacements of the body at the level of the pelvis, while participants stood on a foam rubber mat (40×40×7.5 cm) with eyes open. The distance in millimetres traversed by the pen attached to the sway meter in 30 s was recorded.[31,32] The PPA validity and reliability has been evaluated in several studies and has been shown to predict those community-dwelling people who are at risk of multiple falls with 75% accuracy.[31,33]

In addition, postural sway (area in mm^2) was also assessed on a firm base with eyes open using the same technique as in the PPA. The maximal balance range (MBR) tests (mm), adjusted for height, assessed how far participants could lean forwards and backwards from the ankles without moving the feet or bending the hips.[31,32,34] The coordinated stability test, adjusted for height, assessed participants' ability to adjust body position in a steady and coordinated way while placing them at or near the limits of their base of support.[31,32,34] Gait was measured as the time (in seconds) needed to walk 3 m, turn and walk back at normal pace. The Timed Up and Go Test measured the time required for a person to rise from a chair, walk 3 m, turn, walk back and sit down.[31–33] The Sit to Stand (in seconds) test assessed the time it took participants to rise as fast as possible from a 45-cm high chair five times with their arms folded across the chest.[35–37]

Number of falls

A fall was defined as 'an unexpected event in which the person comes to rest on the ground, floor or lower level'.[32] The number of falls in the previous year was assessed at baseline. Fall frequency during the 1-year follow-up period was monitored with monthly falls diaries and follow-up telephone calls. Questionnaires were given to participants each month, seeking details on the number of falls in the past month, such as the location, cause and any physical injuries suffered, such as bruises, lacerations or fractures. This method for collection of falls data has been used by the investigators in previous studies and is recommended in best practice.[38] Participants were classified as multiple fallers if they fell more than twice during the follow-up period.

Statistical analysis

Statistical analyses were performed using SPSS Statistics Version 17 for Windows (SPSS Inc, Chicago, USA). Data were explored for normal distribution and linearity. Variables with skewed distribution were transformed, after initial assessment of outliers, by logarithim (positive) or square root (negative) transformation prior to further analyses.[39,40] Chi-squared tests were used to assess differences between statin and non-statin users on concomitant medications and to investigate the number of falls during the 12 month follow-up survey.

Differences in the strength, balance and mobility tests between statin and non-statin users were assessed using analyses of covariance while controlling for age and general health.

Results

Characteristics of sample

The mean age of participants was 77.9 years (standard deviation (SD) 4.6), and 270 (54%) were women. Of a possible nine system-related medical conditions, the sample had a mean of 3.1 (SD 1.5.) The most common co-morbidities were arthritis (55.3%), cardiovascular disease (34.8%) and type 2 diabetes (12.3%). Half the sample (n = 250 participants) were taking statin medications. There was no evidence of any differences in age, gender, height (gender specific) and body mass index (gender specific) between those taking and not taking

Table 1 Descriptive characteristics of statin and non-statin users

	Statin† *n* = 250	Non-statin *n* = 249	*P*-value
Gender, frequency (%):			
Male	121 (24.7%)	106 (21.7%)	0.42‡
Female	129 (26.4%)	133 (27.2%)	
Age, mean (SD) (years):			
Males	78 (4.47)	78 (4.59)	0.82
Females	78 (4.60)	77 (4.72)	0.36
Height, mean (SD) (cm)			
Male	170 (6.96)	171 (6.74)	0.76
Female	156 (6.92)	159 (6.61)	0.61
Body mass index, mean (SD) (kg/m^2)			
Male	28.22 (4.78)	27.43 (4.95)	0.31
Female	27.5 (4.21)	26.52 (4.78)	0.19
Health, frequency (%)			
Poor	3 (0.6%)	3 (0.6%)	0.009
Fair	34 (7.0%)	31 (6.4%)	
Good	125 (25.6%)	86 (17.6%)	
Very good	72 (14.8%)	90 (18.4%)	
Excellent	15 (3.1%)	29 (5.9%)	
Number of falls during 12 month follow-up, frequency (%):			
Non-faller (≤1)	201(83.1%)	191 (78.3%)	0.18
Multi faller (≥2 falls)	41 (16.9%)	53 (21.7%)	
Total	242(100%)	244 (100%)	

†Fluvastatin, pravastatin, rosuvastatin, simvastatin or atorvastatin.
‡Yates continuity correction. SD, standard deviation.

statins (Table 1), nor of a difference in gender proportions between the two groups. The non-statin group had a higher proportion of people in very good to excellent health ($P = 0.009$) than the statin group.

Effect of statin use on measures of fall risk

Table 2 shows the mean scores for the strength, balance and mobility tests for the statin and non-statin users (Table 2). After controlling for age and health status, performance only in the MBR test was significantly inferior in the statin users. Results remained after using a Hochberg correction for multiple comparisons.

Effect of statin use on falls during 12-month follow-up period

In all, 149 (30%) participants reported one or more falls in the previous year, and 214 (43%) reported one or more falls during the 1-year follow-up (six participants were lost during follow-up for falls). A Chi-squared test for independence (Table 1) indicated that the proportions of statin users and non-statin users who suffered multiple falls in the follow-up year were not significantly different, relative risk = 0.75 (0.48–1.18).

Discussion

The current study could not confirm associations between use of statins and reduced muscle strength, postural sway and mobility. However our findings did suggest an association between statin use and dynamic leaning balance.

Leaning balance is partly influenced by ankle flexibility and toe plantar flexor muscle strength.[41] The possible myotoxic effect of statins on proximal skeletal muscle strength[7–11] could potentially explain this relationship, however more research is warranted to understand the mechanisms.

Several studies have found a significant age-related decline in the ability of people to reach forward as far as possible without taking a step.[42,43] The most commonly used test is the functional reach test developed by Duncan *et al.*,[42] which has been correlated with age,[42,43] performance in activities of daily living[44] and falls.[45] Reduced dynamic balance is associated with reduced

Table 2 Mean differences between statin and non-statin users on a range of fall risk factors, using analyses of covariance controlling for age and general health

Function test	Non-statin users			Statin users			*F*	Significance (two-tailed)
	n	Mean	SD	*n*	Mean	SD		
Quadriceps strength, kg	248	26.4	11.8	249	27.5	11.9	1.344	0.445†
Floor sway path, mm	244	77.0	39.3	245	81.1	45.4	0.526	0.468
Foam sway path, mm	240	185.0	94.6	239	182.1	94.9	0.083	0.773
Coordinated stability, errors	238	14.7	12.6	238	16.2	13.4	1.591	0.208
Maximum balance range, mm	239	153.0	59.6	243	141.8	51.1	5.744	0.017
PPA score, z-score	239	0.87	0.94	238	0.85	0.91	0.190	0.663
Timed up and go, s	230	9.9	3.4	228	9.6	2.5	2.427	0.120
Sit to stand, s	215	16.0	5.5	229	16.8	5.0	1.914	0.167
Gait speed, m/s	238	8.6	2.8	246	8.9	2.9	1.053	0.305

†Adjusted for gender. For the physiological profile assessment, sway, coordinated stability test, timed up and go, sit to stand and gait speed, high scores indicate impaired performance. For the quadriceps strength and maximum balance range, low scores indicate impaired performance (see Methods section for details of assessment tests). SD, standard deviation.

ability to correct displacements during movement as well as reduced gait speed and step length that can lead to increased fall risk.[46,47]

As far as we are aware, this is the first study to examine the relationship between statin use and prospective falls. There was no indication that statin use increased the number of falls in a 12-month follow-up period. In fact, our findings show a trend indicating statin use may be protective for falls. It is possible that statins may adversely affect some factors associated with falls and ameliorate others. For example, the harmful effect of statins on leaning balance found here and muscle strength in others studies could lead to falls related to loss of balance and/or tripping. On the other hand, the cardioprotective effects of statins[48,49] could reduce falls caused by episodes of dizziness, syncope and/or drop attacks. A larger sample size is needed to determine whether statin use is related differently to different fall types.

The limitations of our study mainly relate to the constraints of the existing dataset, sample size and length of the study. It was necessary to investigate statins as a class as the number taking statins ($n = 250$) was considered too small for analysis of the five different statin medications used, dosage regimens and length of use. This was based on the assumption that the muscle complications are a class effect though some variability may be related to dose, duration or the individual drug. We also did not have data on participants' compliance with statin use during the follow-up period. Previous small studies found myopathic weakness improved on cessation of statins, but symptoms returned within 2 weeks of recommencement of a statin[8,11] with patients complaining of muscle aches, decreased exercise tolerance or unsteadiness when walking or turning.[8,11]

The multiple covariates in the analysis, due to comorbidities and medications, need to be taken into account when concluding that reduced performance is caused by statins alone. As mentioned, higher doses and long-term use may result in a stronger association between statins and muscle strength decline and therefore fall risk. A larger study with greater statistical power may be able to determine if this association exists. Lastly, we acknowledge that our findings are only generalisable to mainly healthy, community-dwelling adults aged between 70 and 90 years.

Conclusion

In a cohort of healthy, older people, the use of statins was not associated with impaired muscle strength, postural sway, reduced mobility or falls. However, statin users performed worse in an MBR test that may potentially increase fall risk. More research is needed to ascertain any (positive or negative) relationship between falls and statin use in older people.

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